IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE:	)	
'318 PATENT INFRINGEMENT LITIGATION	)	**Civ. No. 05-356-(SLR)** **(consolidated)**

DEFENDANTS' JOINT POST-TRIAL REPLY BRIEF

CONFIDENTIAL: FILED UNDER SEAL
SUBJECT TO A PROTECTIVE ORDER

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INTRODUCTION

From the opening statement through post-trial briefing, Defendants have presented the same theory to the Court. Defendants have asserted that it would have been obvious to try another reversible, tertiary amine cholinesterase inhibitor ("CI") as a treatment for Alzheimer's disease ("AD") given that other reversible, tertiary CIs (physostigmine and tacrine) had shown success in treating patients with AD. And there was a reasonable expectation that the drug would work given that galanthamine had proved suitable for use in humans. Galanthamine acted predictably, in accordance with its known function as a reversible tertiary CI. Nothing more is necessary to establish obviousness under *KSR*.

Plaintiffs do not challenge seriously either of these facts but rather seek to divert attention by arguing irrelevancies. First, Plaintiffs focus on "how" Dr. Davis came to her conclusion that galanthamine could be used to treat AD, spending many pages discussing the neuroendocrine window, muscarinic agonists and the nicotinic receptor theory. However, the path Dr. Davis took to get to her invention is legally irrelevant. The only relevant inquiry is whether it would have been obvious to one skilled in the art in 1986 to use galanthamine to treat AD. The prior art unquestionably says yes.[1]

Second, Plaintiffs turn quickly to the secondary considerations of skepticism and failure of others. There indeed was skepticism about CIs as a cure for AD. Rightly so, as CIs do not cure AD. But this skepticism is irrelevant in the search for a *treatment* of AD. Regarding the "failures," Plaintiffs cannot point to a single, reversible tertiary CI that failed to improve the symptoms of AD prior to 1986. While physostigmine and tacrine had drawbacks *vis à vis* duration of action and side effect profiles, this made galanthamine (known to be longer acting than physostigmine and safer than physostigmine and tacrine) all the more obvious choice.

[1] Indeed, Bhasker anticipated Dr. Davis' invention by suggesting using galanthamine to treat AD.

If, however, the Court finds that the patent is not obvious, and that there was no reasonable expectation that galanthamine would work as a treatment for AD, as urged by Plaintiffs, then the patent is not enabled because there is virtually no disclosure in the remarkably slim 2 column patent. The only portion of the patent that Plaintiffs even contend provides reason to believe that galanthamine would work as a treatment for AD is a five paragraph citation to prior art references. There is no disclosure beyond the prior art that would make any scientist of ordinary skill in the art believe that galanthamine would have utility as a treatment of AD.

Plaintiffs therefore are caught in fundamentally inconsistent positions, trying to avoid the prior art that renders the patent obvious on the one hand, and arguing a disclosure of utility in a patent that has no disclosure beyond the prior art that they have vigorously argued provides no expectation of success on the other. The patent is obvious due to the prior art, but if not, it is not enabled by the prior art, as there is nothing in the patent to support enablement. Either way, the patent is invalid.

ARGUMENT

I. CLAIM CONSTRUCTION

A. "Alzheimer's Disease and Related Dementias"

Defendants have stated consistently that AD and "related dementias" mean those dementias related to AD. Throughout this case, Plaintiffs' position was that the term "related dementias" (plural) meant senile dementia (singular) of the Alzheimer's type ("SDAT"). *See, e.g.*, D.I. 322, D.I. 340, D.I. 365 at 7-10. Without explanation, in its post-trial brief, Plaintiffs altered their claim construction, arguing that "related dementias" to AD means SDAT and Down's Syndrome. This is another instance of Plaintiffs shifting and adjusting their theories in this case.

In an attempt to bolster their latest theory, Plaintiffs claim that dementias related to AD encompass diseases "characterized by AD's 'physiological changes' – that is, by the pathology of plaques and tangles." Pl. Br. at 17. As of 1986, an AD diagnosis was based upon the clinical symptoms exhibited in patients, later confirmed pathologically with an autopsy. Levey 95:23-97:3. Thus, the existence of plaques and tangles cannot be the determining factor as to what are considered dementias related to AD as of 1986, because that diagnosis only occurs when treatment is useless, as the patient is dead.

The most common presenting symptoms of AD patients are "dysnomia (forgetting words), presbyophrenia (failure to retain memories but integrity of other cognitive functions), spatial disorientation, personality changes, and gait disorders." PX 752 (Rathmann) at 685. These clinical symptoms include the dementias associated with Huntington's Chorea, multiple strokes (vascular dementia), Lewy body disease, Parkinson's disease, cortical basal degeneration, and progressive cerebral palsy, as well as SDAT and Down's Syndrome.[2] Levey 319:11-16. Defendants proposed this construction,[3] and it is correct scientifically and legally.

B. "Method Of Treating"

Plaintiffs' interpretation of "method of treating" imports further limitations to include in a manner that is "safe, tolerable, and produces clinically meaningful results." Pl. Br. at 17-18. Plaintiffs do not provide any guidance as to what they mean by "clinically meaningful," no doubt because the term "clinically meaningful"[4] does not appear anywhere in the claims or specification of the '318 patent. Rather, the prosecution history makes clear that the utility of the

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[3] *See* Defendants' claim construction briefs, D.I. 323 at 7-10 and D.I. 341 at 1-6.

[4] Dr. Davis provided absolutely no data or evidence in the patent that galanthamine provided a clinically meaningful benefit to AD patients as she never gave galanthamine to any AD patient prior to 1986, and thus, if this definition is adopted, the '318 patent is not enabled.

invention disclosed in the '318 patent rested on the expectation "that treatment with galanthamine [would] result in an improvement in the condition of those suffering from Alzheimer's disease." PX 14 at 2. As the patent specification provides, the condition the invention sought to improve was the cognitive function/functional status of patients.[5] PX 1 at 1:38-42.

Likewise, there is nothing in the '318 patent that mentions the safety or tolerability of galanthamine in AD. *See* PX 1. Rather, the sole focus of the two column patent is that galanthamine hopefully will improve the cognitive function/functional status of an AD patient.[6] Reading the preamble language "method of treating" of claim 1 to include safety and tolerability, makes the other claims of the '318 patent invalid.[7] Claim 5 states: "A method according to claim 4, wherein said dosage rate of 100-600 mg per day." It is well settled that "[a] claim in dependent form shall be construed to incorporate by reference *all the limitations* of the claim to which it refers." 35 U.S.C. § 112 (emphasis added). Furthermore, a dependent claim cannot be broader than the independent claim on which it depends. *Trinity Indus., Inc. v. Road Sys., Inc.*, 121 F. Supp. 2d 1028, 1048 (E.D. Tex. 2000). In order to incorporate all of the limitations of claim 1 (as proposed by Plaintiffs), at a minimum, the administration of 100 mg/day of galanthamine must be "safe, tolerable, and produce clinically meaningful results." Pl. Br. at 17-18.

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[5] This is the construction proposed by Defendants. *See* D.I. 323 at 10-15 and D.I. 341 at 8-14.

[6] Plaintiffs' reliance on extrinsic evidence dated after the patent is irrelevant. *See LG Elecs., Inc. v. Bizcom Elecs., Inc.*, 453 F.3d 1364, 1375 (Fed. Cir. 2006) ("The proper claim construction is the ordinary and customary meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, *i.e.*, as of the effective filing date of the patent application.") (internal quotation omitted).

[7] It is perfectly appropriate to look at claims other than those being asserted in the litigation at issue. "Other claims of the patent in question, *both asserted and unasserted*, can also be valuable sources of enlightenment as to the meaning of a claim term." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) (noting that "[a]lthough each claim is an independent invention, dependent claims can aid in interpreting the scope of claims from which they depend."(internal quotation omitted)). Moreover, with respect to claim construction, a patent's "[c]laims should be so construed, if possible, as to sustain their validity." *Pourchez v. Diatek, Inc.*, 265 F. Supp. 2d 192, 198 (S.D.N.Y. 2003) (citing *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577 (Fed. Cir. 1984)).

REDACTED Plaintiffs' attempt to incorporate FDA requirements into the claim limitations should be rejected as the PTO is not concerned with the clinical, safety or tolerability requirements of the FDA. *In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995).

II. CLAIM 1 IS ANTICIPATED BY BHASKER, AND THUS IS INVALID

Plaintiffs' brief clarifies what is not in dispute. Throughout discovery, summary judgment briefing and into trial, two of Plaintiffs' main attacks against Bhasker remarkably were that it was not a printed publication because it was not publicly available and it could not have been describing AD because the course of the illness is not rapidly downhill. D.I. 319 at 5-8. These stances evidence how far Plaintiffs would go to try to avoid the anticipatory nature of Bhasker. Now, Plaintiffs have dropped both arguments. Further, Plaintiffs do not argue that Bhasker is not enabled. Pl. Br. at 18-22. Plaintiffs also do not dispute that Bhasker discloses the administration of a small amount of galanthamine to patients and that it discloses the administration of a therapeutically effective amount of galanthamine to improve higher cortical function. Pl. Br. at 18-22; *see* Def. Br. at 18; Levey 222:6-223:2. The *only* point of contention is whether Bhasker "describe[s] galanthamine as a treatment for AD." Pl. Br. at 19-20.

A. Bhasker Describes the Treatment of Alzheimer's Disease

After arguing for years that Bhasker disclosed no treatment for dementia, Plaintiffs now argue that Bhasker contains a limitation to the treatment of a particular type of dementia, arrested dementia, to the exclusion of progressive dementia. Put another way, Plaintiffs do not contest that Bhasker discloses the use of galanthamine as a treatment, but they argue it was not disclosed as a treatment for progressive dementia, the type that includes AD.

First, Bhasker is titled "Medical Management of Dementia," and discusses three types of dementia: reversible, arrested and irreversible/progressive. DX 483; Levey 210:11-210:14. There is no dispute that AD is a dementia and, in fact, the leading cause of dementia. *Id.* 207:25-208:6. Accordingly, there is no dispute that one of ordinary skill in the art in 1986 would read Bhasker's reference to dementia, and specifically progressive dementia, as encompassing AD. *Id.* 213:2-213:9; Domino 488:14-488:17; Coyle 990:21-991:2. Because it is clear that Bhasker discusses dementia, which includes AD, Plaintiffs are left only to argue that the paragraphs of Bhasker discussing treatments of dementia singled out arrested dementia and excluded others.

In the paragraphs leading up to the discussion of galanthamine, Bhasker speaks consistently only of progressive dementia. In his discussion of "restoration of higher cortical functions," through the administration of galanthamine, he plainly is continuing to refer to progressive dementias. DX 483-02. There is no dispute that "the restoration of higher cortical functions" refers to cognitive functions that are implicated in progressive dementia. Levey 216:17-216:19. Thus, Bhasker's reference to dementia and the restoration of higher cortical functions necessarily includes AD.[8]

B. Plaintiffs' Arguments Rely on Distortions of the Record

1. Plaintiffs rely on a typographical error and out-of-context excerpts

Plaintiffs' argument that Bhasker's only disclosure of galanthamine as a treatment only for arrested dementia relies on clear typographical error or misstatement. The context in which the disputed transcription[9] occurs makes clear the true import of the testimony cited. The disputed quote concerns Dr. Levey's testimony about the paragraph in Bhasker dealing with

[8] After Defendants pointed out that the prior art need not contain specific reference to the exact term AD, *see* Def. Br. at 19, Plaintiffs dropped this argument as well.

[9] Plaintiffs refused to make the change on the errata sheet at the time and now it is clear why. Even if Dr. Levey simply misspoke, arrested dementia is not what he intended, as set forth below.

galanthamine as a treatment: "it's absolutely inherent in [Bhasker's] paper where he's putting this in context that he's suggesting cholinesterase inhibitors might be tried for treating dementia, arrested [sic] dementia." Levey 219:20-220:3. The context makes clear that Dr. Levey was referring to progressive dementia. For example, the question immediately following Dr. Levey's answer was: "And **progressive dementias** include Alzheimer's disease, is that right?" *See id* 220:4-6 (emphasis added). A few questions later Dr. Levey again reiterated that Bhasker addressed progressive dementia:

> Q: Does the Bhasker reference make a reference to a treatment of Alzheimer's disease and related dementias?
> A: Yes, it does.
> Q: Why do you say that?
> A: Because as we just walked through it, it talked about treatment of patients with **progressive dementia**, which includes Alzheimer's disease. It's inherent in that.

Id. 221:24-222:5 (emphasis added).[10]

Plaintiffs' counsel plainly understood Dr. Levey's answer to refer to progressive dementia. On cross examination, for example, Plaintiffs asked whether "Bhasker describe[d] galanthamine as treatment for every type of [progressive dementia]," to which Dr. Levey responded that Bhasker was suggesting galanthamine "as a treatment broadly for the category **progressive dementia** without going into etiology." *Id.* 319:21-320:3 (emphasis added). Dr. Levey then continued to explain, on further cross examination, that the article concerned treatment of progressive dementia of which AD was one type. *See id.* 320:4-321:19; *see also* Domino 488:21-489:3. That Plaintiffs ignore the bulk of this testimony to exploit a (known) mistranscription or misstatement demonstrates the weakness of their position.

[10] *See also* Levey 222:6-223:7; 216:17-216:19 ("Higher cortical functions refers to the cognitive functions that are implicated in – progressive dementia and Alzheimer's disease.").

Plaintiffs rely on Bhasker's statement that "[w]ith regard to progressive dementia, there appears little to offer" as "[o]nly management and no treatment is possible," while ignoring the statement a few paragraphs later that although treatment, *i.e.*, "restoration of higher cortical functions," was "once considered to be impossible . . . it has lately gained importance." Pl. Br. at 19-20.[11] As Dr. Levey noted, Bhasker explains that, although it "appeare[d]" that no treatment was available—it once was considered impossible—there was now hope on the horizon in the form of cholinesterase inhibitors such as galanthamine. *Id.*; Domino 488:21-489:2.

2. Bhasker need not have known of the cholinergic deficit hypothesis in 1974

Plaintiffs make much of the inconsequential fact that the 1974 article appeared prior to major writings on the cholinergic deficit hypothesis. Most fundamentally, the cholinergic deficit hypothesis is not an element or limitation of Plaintiffs' claim and it need not be described in Bhasker's article. *In re Paulsen*, 30 F.3d 1475, 1478-79 (Fed. Cir. 1994) (noting that anticipation only requires that each "limitation of the claimed invention be disclosed in a single prior art reference"). That Bhasker in 1974 may not have possessed the scientific explanation of "cholinergic deficit hypothesis" that was available to anyone of ordinary skill in the art in 1986 is of no relevance. The method of treating progressive dementia was disclosed even though the full scientific explanation was not. *See Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) ("[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.").

[11] Plaintiffs rely on the reference to neostigmine in conjunction with galanthamine as evidence of teaching away from a treatment of AD because neostigmine "does not readily get into the brain." Pl. Br. at 20. However, "whether a reference 'teaches away' from the invention is inapplicable to an anticipation analysis." *Celeritas Techs. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998). Plaintiffs neither cite nor refute the applicability of that precedent to this issue. Further, Plaintiffs ignore the fact that the entire article is directed towards dementia and particularly progressive dementia.

In analyzing Bhasker, the proper vantage point is what one of ordinary skill in the art understood in 1986. *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) ("[R]ecognition by a person of ordinary skill in the art before the critical date of the [patent] is not required to show anticipation by inherency. The district court therefore did not err in allowing for later recognition of the inherent characteristics of the prior art."). That Bhasker may not have understood that galanthamine repaired a "cholinergic deficit" is irrelevant. *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570 (Fed. Cir. 1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests.").

Persons of ordinary skill would have understood each element of Plaintiffs' claim because they were well aware of the cholinergic deficit hypothesis and all of the prior art relevant thereto. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986) ("The person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art."); Levey 224:19-224:23. As such, Defendants have presented clear and convincing evidence that a person of ordinary skill in the art would read Bhasker in 1986 as anticipating Claim 1 of the '318 patent.

III. CLAIMS 1 AND 4 ARE OBVIOUS, AND THUS ARE INVALID

Plaintiffs' entire argument against obviousness is a game of subterfuge and confusion. Plaintiffs devote page after page of their brief (and most of their time at trial) discussing the nicotinic receptors vs. muscarinic receptors and which drugs are strong muscarinic agents vs. which are weak ones. All of this is a red herring. The point is this: the intrasynaptic approach calls for using a reversible, tertiary amine CI. Levey 107:13-108:10; 130:14-18; 178:5-25. That

is a CI that is reversible[12] and crosses the blood-brain barrier. If it does this, then it inhibits acetylcholinesterase, the enzyme that breaks down acetylcholine, leaving more acetylcholine in the brain and thus improving the symptoms of AD. *Id.* It is as simple as that.

Physostigmine and tacrine were both reversible, tertiary amine CIs, and, predictably, both were shown to improve the symptoms in AD patients in studies done prior to 1986. Levey 131:1-158:5; 179:1-4. That physostigmine was not ultimately sold as an AD drug is of no import. Both physostigmine and tacrine provided "proof of concept" for the intrasynaptic approach, something that was lacking in the pre-synaptic and post-synaptic approaches prior to 1986. Levey 128:21-130:10; 164:14-25; Domino 386:3-21.

This proof of concept led directly to galanthamine, which had the same mechanism of action but a better therapeutic profile. DX 70; DX 71; PX 743; PX 744. Galanthamine had a longer duration of action than physostigmine and a better side effect profile than both physostigmine and tacrine. *Id.*; Levey 205:11-23. Plaintiffs attempt to distinguish between whether something works in the periphery or in the brain, and claim that galanthamine was known to have peripheral effects. But this argument misses the point: Galanthamine was a known reversible, tertiary amine cholinesterase inhibitor, meaning it got into the brain (a point Plaintiffs do not dispute). Further, the fact that galanthamine also had been used for peripheral disorders (such as myasthenia gravis) does not detract from its ability to act as a CI, but rather encourages one to use it to treat AD, because that teaches that it gets into the brain and can be used safely, without the concern of peripheral side effects (unlike physostigmine and tacrine). Levey 180:9-184:2.

Put simply, using galanthamine to treat AD is no more than the predictable use of galanthamine according to its established function. This is exactly what the cholinergic deficit

[12] An irreversible CI essentially becomes a nerve agent and can kill humans. Domino 450: 2-12.

hypothesis called for generally, and what the intrasynaptic approach predicted specifically. Under *KSR*, nothing more is required. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007).

A. How Dr. Davis Arrived at Her "Invention" is Irrelevant

Plaintiffs go to great lengths in their brief, as they did at trial, to explain that Dr. Davis utilized the "neuroendocrine window"[13] to come up with the idea of using galanthamine to treat AD, undoubtedly attempting to make an obvious concept appear novel. However, Dr. Davis' reasons for her invention are irrelevant and immaterial in determining obviousness. *See Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000) ("[T]he path that leads an inventor to the invention is expressly made irrelevant to patentability by [35 U.S.C. § 103]."). "Because patentability is assessed from the perspective of the hypothetical person of ordinary skill in the art, information regarding the subjective motivations of [Dr. Davis are] not material." *Id.* All of Plaintiffs' noise about the various receptors and the nicotinic theory, therefore, is just that. The only relevant question is whether using galanthamine to treat AD would have been obvious to one skilled in the art in 1986. As set forth below and in Defendants' Opening Brief, the answer is most decidedly yes.

B. Plaintiffs' Assertions Regarding Skepticism, Failures and Muscarinic Agonists Are Misleading and/or Irrelevant

Plaintiffs attempt to attack the intrasynaptic approach, arguing the post-synaptic (using muscarinic agonists) approach was more attractive in 1986. Plaintiffs' attack falls short because, as is evident by the focus of scientists on CIs prior to 1986, the intrasynaptic approach was pursued aggressively prior to 1986. At the same time, however, everyone in the field knew that CIs were never going to provide a cure for AD, rather simply provide temporary (up to about a

[13] Contrary to Plaintiffs' assertion in their brief, Dr. Davis **did not** invent the neuroendocrine window. Davis 691:16-20.

year) treatment, which is exactly what galanthamine does. As Dr. Levey put it, CIs were not the "homerun," and while an AD treatment was important, scientists continued looking for that "homerun." Levey 149:16-150:17. Thus, it is not surprising that scientists experimented with other approaches, including the post-synaptic approach. Much of the skepticism that Plaintiffs rely on, therefore, is directed to whether any CI would be a cure or whether there was a CI with a good therapeutic profile, not whether a CI could treat AD.

Some scientists' pursuit of other approaches, therefore, does not make using galanthamine to treat AD any less obvious or the CI approach any less viable.[14] Indeed, the intra-synaptic approach is the only one with proof of concept[15] prior to 1986. Plaintiffs cannot point to a single reversible, tertiary CI that failed prior to 1986. The "failures" that Plaintiffs rely on have nothing to do with the intrasynaptic approach and certainly do not and did not undermine the approach.

The failure of the pre-synaptic approach would not have discouraged a person of ordinary skill in the art from pursuing reversible, tertiary CIs. As Bartus explained, "[t]he lack of efficacy with precursors, therefore, should not be considered an issue relevant to the viability of the cholinergic hypothesis, for in fact, this effect had been anticipated early in part due to the very cholinergic deficiencies which support the cholinergic hypothesis." PX 741 at 427.

Plaintiffs' focus on the post-synaptic approach/muscarinic and nicotinic receptors is another attempt to muddy up what is a very straightforward analysis and conclusion.[16] Muscarinic agonists and CIs are two entirely different classes of neurochemicals with completely different mechanisms of action. What happens in the muscarinic and nicotinic receptors has no

[14] That Drs. Domino and Levey may haven pursuing "cures" to AD does not impact the obviousness of CIs as a treatment for AD.
[15] "Proof of concept" means having experimental evidence to support a hypothesis. Levey 164:14-25.
[16] *See* DX 1200 for a demonstrative of the cholinergic system and the different synaptic approaches.

impact on scientific conclusions about CIs. CIs do not act on the nicotinic or muscarinic receptors – they simply inhibit cholinesterase, thus preserving acetylcholine. PX 751 at 688.[17] Contrary to Plaintiffs' unsupported assertion, the cholinergic deficit hypothesis was not "focused on the central muscarinic system, based on the association between the muscarinic system and memory," but rather was focused on addressing the known deficit of acetylcholine in AD patients. Pl. Br. at 35; *compare* PX 663 at Fig. 1; PX 751 at 688; Def. Br. at 4-15. The intrasynaptic approach addresses this deficit by inhibiting cholinesterase through CIs like galanthamine. Instead of slowing down the degradation of acetylcholine (like CIs), muscarinic agonists attempt to address the deficit by mimicking the action of acetylcholine by "directly stimulat[ing] the post-synaptic [receptor] -- by binding to muscarinic receptors or nicotinic receptors." Levey 129:9-18. This approach, known as the post-synaptic approach, has nothing to do with the intrasynaptic approach generally or galanthamine's ability, as a reversible, tertiary CI, to treat AD specifically.

In sum, the only approach with proof of concept prior to 1986 was the intrasynaptic approach. Neither the failure of the pre-synaptic or the post-synaptic approaches nor the skepticism about CIs being the "home run" would have discouraged scientists from pursuing the intrasynaptic approach or made using galanthamine as an AD treatment non-obvious.

C. *KSR* Lowered the Bar to Establish Obviousness

As the Supreme Court in *KSR* recognized, "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her

[17] Dr. Davis did not discover the role of nicotinic receptors in the cholinergic system. Dr. Coyle's *Science* article explained "acetylcholine is stored within vesicles in the nerve terminal and released into the synaptic cleft upon depolarization." PX 663 at Figure 2. Upon release, "[a]cetylcholine diffuses across the cleft to activate muscarinic receptors, the predominant receptor in the brain, **or nicotinic receptors**." *Id.* (emphasis added). "The action of acetylcholine is rapidly terminated by the enzyme acetylcholinesterase." *Id.*

technical grasp." *KSR*, 127 S. Ct. at 1732.[18] In such circumstances, "the fact that a combination was **obvious to try** might show that it was obvious under § 103." *Id.* at 1742 (emphasis added). District courts have "characterized this decision as 'generally lower[ing] the bar for alleged infringers attempting to establish obviousness.'" *Seitz v. Envirotech Sys. Worldwide Inc.*, Civ. A. No. H-02-4782, 2007 U.S. Dist. LEXIS 44272, at *26 (S.D. Tex. June 19, 2007) (citations omitted). It is not surprising then, that the number of patents being found to be invalid on obviousness grounds is outnumbering those that are being upheld since *KSR* at a pace of nearly 3:1. As of today, there have been 16 Federal Circuit and District Court cases[19] in which a court (7 from the Federal Circuit) substantively held that a patent was obvious, while there are only 6 cases[20] in which a court (only 1 from the Federal Circuit) substantively held that a patent was non-obvious after *KSR* was decided. Clearly the trend is heavily in Defendants' favor.

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[18] *Compare In re Omeprazole Patent Litig.*, No. M-21-81, 2007 U.S. Dist. Lexis 39670, at *457 (S.D.N.Y. June 1, 2007)(finding a patent non-obvious where "there were thousands and thousands of permutations and paths facing a person of ordinary skill"). As of 1986, the evidence showed that there were only three known reversible, tertiary CIs: tacrine, physostigmine, and galanthamine. PX 1401(a). Even if one were to include the pre-synaptic and post-synaptic approaches, there are only two pre-synaptic compounds (choline and lecithin) and only one post-synaptic compound (arecoline) that were being pursued as of 1986. *See* PX 1401(a). This is hardly "thousands and thousands of permutations and paths" facing a person of ordinary skill in the art. Although this is not the relevant or correct inquiry, even if one were to look at every single possible approach identified by Plaintiffs being pursued to treat AD, there were only ten such approaches prior to 1986. *Id.* Again, this finite number hardly constitutes "thousands and thousands of permutations and paths."

[19] *Syngenta Seeds, Inc. v. Monsanto Co.*, No. 2006-1203, 2007 U.S. App. Lexis 10496 (Fed. Cir. May 3, 2007); *Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157 (Fed. Cir. May 9, 2007); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. Mar. 22, 2007); *Eaton Corp. v. ZF Meritor, LLC*, No. 03-74844, 2007 U.S. Dist. Lexis 39384 (E.D. Mich. May 31, 2007); *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, No. 05-1490, 2007 U.S. App. Lexis 16245 (Fed. Cir. June 9, 2007); *Semiconductor Energy Lab. Co. v. Chi Mei Optoelectronics Corp.*, No. C 04-04675, 2007 U.S. Dist. Lexis 44288 (N.D. Cal. June 19, 2007); *Single Chip Sys. Corp. v. Intermec IP Corp.*, No. 04CV1517, 2007 U.S. Dist. Lexis 50622 (S.D. Cal. June 29, 2007); *McNeil-PPC, Inc. v. Perrigo Co.*, No. 05 Civ. 1321, 2007 U.S. Dist. Lexis 50255 (S.D.N.Y. July, 3, 2007); *Daiichi Sankyo, Co. v. Apotex, Inc.*, No. 2006-1564, 2007 U.S. App. Lexis 16576, (Fed. Cir. July 11, 2007); *In re Icon Health & Fitness, Inc.*, No. 2006-1573, 2007 U.S. App. Lexis 18244 (Fed. Cir. Aug. 1, 2007); *Asyst Techs., Inc. v. Empak, Inc.*, No. C98-20457, 2007 U.S. Dist. Lexis 59100 (N.D. Cal. Aug. 3, 2007); *Craig v. Foldfast, Inc.*, No. 06-61009-CIV, 2007 U.S. Dist. Lexis 58548 (S.D. Fla. Aug. 9, 2007); *Adanceme, Inc. v. Rapidpay, LLC*, No. 6:05CV4242007 U.S. Dist. Lexis 59381 (E.D. Tex. Aug. 14, 2007); *In re Trans Tex. Holdings Corp.*, No. 2006-1599, 2007 U.S. App. Lexis 19909 (Fed. Cir. Aug. 22, 2007); *Ricoh Co. v. Quanta Computer Inc.*, No. 06-C-462, 2007 U.S. Dist. Lexis 62415 (W.D. Wis. Aug. 21, 2007); *PBI Performance Prods., Inc. v. Norfab Corp.*, No. 05-4836, 2007 U.S. Dist. Lexis 63733 (E.D. Pa. Aug. 29, 2007).

[20] *See In re Omeprazole Patent Litig.*, 2007 U.S. Dist. Lexis 39670; *Stryker Trauma, S.A. v. Synthesis*, CNo. 01-cv-3879, 2007 U.S. Dist. Lexis 47468 (D.N.J. June 27, 2007); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, No.

1. An Invention That Performs In A Predictable Manner In Accordance With Its Known Functions Is Obvious And Invalid Under 35 U.S.C. § 103

"When a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR*, 127 S. Ct. at 1740, *citing Sakraida v. Ag Pro, Inc.*, 425 U.S. 273 (1976) (internal quotations omitted). As the Federal Circuit explained, where a "patentee claims a combination of old prior art elements as its asserted point of novelty," "the combination must be a non-trivial advance over the prior art" to be non-obvious. *Egyptian Goddess, Inc. v. Adi Torkiya*, No. 2006-1562, 2007 U.S. App. Lexis 20599, at *6, n.2 (Fed. Cir. Aug. 29, 2007).[21]

2. Claim 1 of the '318 Patent Is Obvious Because Galanthamine Treats AD Predictably And In Accordance With Its Known Functions

Plaintiffs do not contest that all of the claimed elements of the '318 patent existed in the prior art. Pl. Br. at 3. Instead, Plaintiffs have attempted to shift the Court's attention away from the predictable, well-established manner in which reversible, tertiary CIs treat AD symptoms by introducing a discussion of the role of nicotinic receptors in the cholinergic system. Pl. Br. 9-11.

The parties agree that researchers sought to address the deficit of acetylcholine in AD through pharmacological means. Pl. Br. at 6; Def. Br. at 7-12. Plaintiffs did not dispute the fact that CIs treat AD's symptoms by slowing down the degradation of acetylcholine by inhibiting the enzyme acetylcholinesterase ("AchE"). *See* Def. Br. at 7-12. Most revealing, Plaintiffs did not dispute at trial or in their brief that, prior to 1986, tacrine and physostigmine, reversible,

06-1329, 2007 U.S. App. Lexis 15349 (Fed. Cir. June 28, 2007); *Sundance, Inc. v. De Monte Fabricating, Ltd.*, No. 02-73543, 2007 U.S. Dist. Lexis 41364 (E.D. Mich. June 7, 2007); *Muniauction, Inc. v. Thomas Corp.*, Civ. A. 01-1003, 2007 U.S. Dist. Lexis 55433 (W.D. Pa. July 31, 2007); *Lucent Techs. Inc. v. Gateway, Inc.*, Civ. No. 02CV2060-B, 2007 U.S. Dist. Lexis 57135 (S.D. Cal. Aug. 6, 2007).

[21] Indeed, Dr. Rainer was using galanthamine to treat AD *circa* 1986 (DX 169) and Dr. Domino suggested pursuing galanthamine to treat AD in his 1988 article, without knowing of the '318 patent. Domino 413:20-414:14.

tertiary CIs were shown to improve the symptoms of AD.[22] *See* Pl. Br. at 32-33; *compare* Def. Br. at 7-12, 23-24.[23] Plaintiffs do not and cannot dispute that galanthamine, like physostigmine and tacrine, works according to its known function as a reversible, tertiary CI, and predictably treats AD.

3. Plaintiffs' Reliance On *Takeda* Is Misplaced.

Plaintiffs rely on the post-*KSR* case of *Takeda Chem. Indus., Ltd. v. Alphapharm, Pty., Ltd.*, 2007 U.S. App. Lexis 15349. There, the court "found nothing in the prior art to narrow the possibilities of a lead compound [for the treatment of diabetes] to compound b," which was disclosed in the prior art. *Id.* at *22. Notably, "compound b was not identified as one of the three most favorable compounds. On the contrary, compound b, was singled out as causing 'considerable increases in body weight and brown fat weight.'" *Id.* at *17.

Unlike *Takeda*, Dr. Davis merely followed the prior art directly to galanthamine, which is a second generation drug, *i.e.*, a follower rather than a lead compound. It is undisputed that physostigmine and tacrine were considered prototypes or first generation CIs to treat AD. Indeed, the prior art characterized physostigmine "as a useful pharmacological model" and encouraged "further studies with this drug **prototype**." PX 752 at 684, 688 (Rathmann 1984) (emphasis added). As Dr. Domino explained, the prior art directed a person of ordinary skill in the art to "something in the same general family of action as physostigmine. That is a reversible

[22] To the extent Plaintiffs do denigrate the wealth of prior art showing that physostigmine, due to its mechanism of action as a reversible, tertiary CI, has the ability to treat AD in humans, this stance is problematic for Plaintiffs. Pl. Br. at 32. The '318 patent specification discloses a physostigmine study where the drug was shown to reverse a cholinergic deficiency in lesioned mice. PX 1 at 2:45-57. Dr. Davis disclosed that "[d]rugs that can normalize these abnormalities would have a reasonable expectation of efficacy in Alzheimer's disease." *Id.* This disclosure is what Plaintiffs rely upon to enable the '318 patent. Pl. Br. at 35-46. However, this position cannot be squared with their argument against obviousness that physostigmine failed as a treatment and its mechanism of action, as a reversible, tertiary CI, would have no bearing as to whether a person of ordinary skill would expect galanthamine to treat AD symptoms, as a reversible, tertiary CI. Pl. Br. at 31-32.

[23] Further, Plaintiffs did not respond to the evidence presented by Defendants at trial and in their Opening Brief showing that the so-called negative studies with physostigmine were not due to the failure of the drug's mechanism of action, but rather to poor study design or were simply mischaracterized as failures. Def. Br. at 7-12; 23-24.

cholinesterase inhibitor. That refers to also a compound that has a tertiary amine that readily penetrates the blood/brain barrier." Domino 390:5-9. Indeed, Dr. Davis described the prior art as "virtually a prescription" for galanthamine. B. Davis 789:5-791:16. Thus, unlike *Takeda*, here there were lead compounds, tacrine and physostigmine. As such, the possibilities were narrowed down to galanthamine. *Takeda*, therefore, supports an obviousness finding here.

D. Galanthamine Was an Obvious Substitute to Treat AD

Plaintiffs try to claim that galanthamine's side effect profile, potency and duration of action would lead one of ordinary skill away from, and not toward, galanthamine when looking for a substitute for physostigmine. Plaintiffs are wrong.

1. Safety and Tolerability

Plaintiffs failed to refute the wealth of literature showing that galanthamine was safely tolerated in humans. Def. Br. at 14, 30, 34. Indeed, Dr. Coyle, Plaintiffs' own expert, agreed that prior to 1986, galanthamine "was known to have minimal side-effects," less side-effects than physostigmine, and was reported to be safe and tolerable in humans. Coyle 974:2-23. Rather Plaintiffs rely on these statements as a means of establishing that the '318 patent was enabled. PX 46. Surely, galanthamine's side effect profile would be attractive.

2. Potency

Plaintiffs claim that galanthamine is not as potent as physostigmine and thus would not be an attractive substitute. Defendants do not dispute that physostigmine is more potent than galanthamine. What is critical to keep in mind is Dr. Domino's warning not to confuse potency with efficacy: efficacy refers to whether a compound is effective, while potency merely refers to a dose. Domino 415:5-417:12. Therefore, a person of ordinary skill in the art would not have been dissuaded from using galanthamine because its therapeutic window is broader than

physostigmine's. This means there is a larger range of doses of the drug that can be given safely. Coyle 981:23-982:3. This directly refutes Plaintiffs' argument that by increasing the dose of galanthamine (to address potency concerns), one would also increase the side effects. Coyle 982:4-9. The prior art taught that doses of oral physostigmine in the range of .5 to 2.0 mg were shown to treat AD. PX 670 at 451. Assuming, *arguendo,* that galanthamine has an identical duration of action to physostigmine, a person of ordinary skill would have to give 5 to 20 mg of galanthamine to successfully inhibit AchE. Domino 416:18-20.

Plaintiffs do not dispute that the Daskalov reference discloses that galanthamine can be chronically administered orally in doses ranging from 3-20 mg to treat aphasia, an AD symptom, without causing intolerable side effects. PX 754 at 9. Most importantly, the Daskalov reference taught that those doses would have a "stimulating effect, exciting the central nervous system as a result from acetylcholine accumulation in the brain cortex," because such doses inhibit AchE. *Id.* Essentially, these doses of galanthamine, which are ten times greater than physostigmine, can safely act as a CI in the brain. Accordingly, a person of ordinary skill would not be dissuaded from using galanthamine as a treatment for AD due to its potency.[24]

3. Duration of Action

Although Plaintiffs argue that galanthamine was only as long-acting as physostigmine, the prior art shows otherwise. Physostigmine was reported to have a duration of action from less than one hour to a maximum of two hours. PX 752 at 688; Pl. Br. at 36. Conversely, the prior art teaches that galanthamine's duration of action is 6 to12 hours. PX 1181 (Pernov) at MYLAN(GAL) 05987. Daskalov reported that galanthamine had a six to eight hour

[24] Plaintiffs claim that a person of ordinary skill in the art would already know how to safely and effectively dose galanthamine in humans because the prior art disclosed that galanthamine could be administered orally and in dosage ranges that fall within the range of 10-2000 mg. Pl. Br. at 43; Def. Br. at 30-31. Thus, Plaintiffs admit that Claim 4 is obvious. This is a different analysis from the enablement analysis regarding Claim 4. As set forth *infra*, Dr. Davis was required to enable the full scope of claim 4 (10-2000mgs.), which she did not and could not do.

duration of action, falling within the 6-12 hour range established by Pernov. PX 743 at 9 Galanthamine's significantly longer duration of action, therefore, makes it an ideal substitute for physostigmine.

E. None Of The Secondary Considerations Rebuts An Obviousness Finding

1. Commercial Success

A patentee offering evidence of "commercial success" bears the burden of showing that there was, in fact, commercial success. *In re Paulsen*, 30 F.3d at 1482.

REDACTED

See Medpointe Healthcare, Inc. v. Hi-Tech Pharmacal Co., 115 Fed. Appx. 76, 80-81 (Fed. Cir. 2004).

REDACTED

Accordingly, no weight should be afforded to Plaintiffs' baseless assertion of commercial success.

2. Unexpected Benefits

Plaintiffs have identified two allegedly unexpected benefits: (1) galanthamine's second mechanism of action as a nicotinic allosteric modulator; and (2) galanthamine slows the progression of AD. Plaintiffs do not dispute the fact that they have the burden in proving that the claimed unexpected benefits *actually* did occur. *See* Def. Br. at 36.

Plaintiffs failed to cite any evidence that galanthamine's second mechanism of action provides a clinically significant benefit to AD patients. Raskind 1219:9-21.

REDACTED

Likewise, Plaintiffs failed to show proof that galanthamine actually slows the disease progression of AD. Again, Janssen's own prescribing information states: "There is no evidence that galanthamine alters the course of the underlying dementing process." Def. Br. at 37. In a last-ditch attempt to avoid a finding of obviousness, Plaintiffs rely on a flawed, biased study to establish that galanthamine slows the progression of AD. The "study" was paid for by Janssen, four of the five authors were Janssen employees or consultants (including Dr. Raskind), and, most importantly, Dr. Raskind admitted that the reported findings may have been the result of a placebo effect because the study was open-label. *See* PX 706 at SYN RAZ 0023388; Raskind 1214:4-14; 1214:17-19. This "study" is hardly the sort of objective evidence that supports a finding of non-obviousness.

3. Long-felt, but Unmet, Need

Plaintiffs' argument that galanthamine met a long-felt, but unmet need in 1986 defies their own characterization of the facts. It is undisputed that galanthamine is not a cure for AD, as that need still goes unmet. Galanthamine only provides a temporary alleviation of the symptoms in some AD patients. Def. Br. at 32-33. If the need to be met was using a CI to improve cognition in AD patients, that need was met by tacrine and physostigmine prior to 1986. If the need was access to an FDA-approved CI, that need was met first by tacrine (1993), then Aricept (1996) and finally Exelon (2000). Levey 247:21-248:16; Boghigian 570:22-571:2. Razadyne was not approved by the FDA until 2001. In the context of drugs for human therapy, a "long-felt need" is not present where there are already several other drugs of the same class in the marketplace. *See Aventis Pharma Deutschland GMBH v. Lupin Ltd.*, Civ. A. No. 2:05cv421,

2006 U.S. Dist. LEXIS 48246 at * 137 (E.D. Va. July 17, 2006) (finding that there "simply was no 'long-felt need'" for a drug where there were already "several effective" drugs of the same class already on the market).

4. Licensing and Acquiescence

REDACTED

Plaintiffs simply cannot have it both ways.

REDACTED

There are many legal and commercial reasons that an ANDA filer may file a paragraph III certification. To name just a few, an ANDA filer may not be a first-filer under Hatch-Waxman, or since the '318 patent expires in December 2008, a company may feel that the chances of getting to a final decision by the Federal Circuit before the patent expires are slim. It is improper for Plaintiffs simply to speculate that simply by filing paragraph III certifications, those companies are acquiescing in the validity of the patent.

IV. CLAIMS 1 AND 4 ARE NOT ENABLED, AND THUS ARE INVALID

A. *Rasmusson* Is Binding Precedent

Plaintiffs do not dispute that the enablement requirement requires the patent to have utility. Perhaps that is so because "[i]t is well-established that the 'use' element of the enablement requirement under 35 U.S.C. § 112 incorporates the utility requirement of 35 U.S.C.

§ 101." *Pfizer, Inc. v. Teva Pharms. USA, Inc.*, Civ. A. No. 04-754, 2007 U.S. Dist. Lexis 20190, at *60-62 (D.N.J. Mar. 20, 2007) (for purposes of the utility requirement of 35 U.S.C. § 101, "in vitro data can be sufficient to establish utility of a chemical compound. In vivo data is not always required." For example, "in vitro data can suffice to establish practical utility when the disclosed in vitro data is supplemented by the similar in vitro and in vivo pharmacological activity of structurally similar compounds." (internal quotations omitted)). Moreover, even in *In re Brana*, which Plaintiffs rely upon heavily, the patentee offered proof of utility through "statistically significant tests with standard experimental animals." 51 F.3d at 1567-68.

Plaintiffs spend much of their brief criticizing *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318 (Fed. Cir. 2005), but the case remains good law. Plaintiffs try to limit its applicability to proceedings before the PTO prior to patent approval, but they cite no case so restricting *Rasmusson*. Indeed, precedent suggests otherwise. *See* 3 Chisum on Patents, § 7.03 (2006) (citing *Rasmusson*, 413 F.3d at 1322-23, among other cases, to explain the relationship between the utility requirement and the "how-to-use aspect of the enablement requirement" without noting any such limitation); *Mangosoft, Inc. v. Oracle Corp.*, 421 F. Supp. 2d 392, 405 (D.N.H. 2006) (citing *Rasmusson* and the enablement requirements in a patent infringement action).

Indeed, the Federal Circuit applied the principles enumerated in *Rasmusson* in *Northpoint Tech., Ltd. v. MDS America, Inc.*, 413 F.3d 1301, 1310 (Fed. Cir. 2005). In that case, the court concluded that the patent at issue, which was not subject to an *inter partes* proceeding, was invalid because it failed to enable the invention as required by 35 U.S.C. § 103. *Id.* at 1310. As in *Rasmusson*, the court found that "the teachings set forth in the specifications provide no more

than a plan or invitation for those of skill in the art to experiment.," and thus ruled the patent invalid. *Id.* (citation and internal quotations omitted).

With respect to enablement, the lack of utility defense is appropriate "when there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762 (Fed. Cir. 1984). The utility requirement, under 35 U.S.C. § 103, exists because "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." *Brenner v. Manson*, 383 U.S. 519, 536 (1966). As the Federal Circuit explained, "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997) (citations omitted). Accordingly, it is evident that enablement is a "[p]atent invalidity ... statutory defense," rather than simply "a regulatory duty" subject to the purview of the PTO. *Lannom Mfg. Co. v. U.S. Int'l Trade Comm'n*, 799 F.2d 1572, 1579 (Fed. Cir. 1986).

Plaintiffs' claim that Defendants argue that the enablement requirement mandates large scale human testing of galanthamine to be enabled is wrong. Pl. Br. at 46-47. Following settled law, Defendants consistently have argued that the '318 patent was required to contain some data that galanthamine works as claimed, unless a person of ordinary skill in the art would accept without question that the claimed invention would work. *Rasmusson*, 413 F.3d at 1323.

B. Plaintiffs Do Not Fulfill the Requirements of *Rasmusson*

Plaintiffs do *not* contend they satisfy the first prong of the Rasmusson test: that someone skilled in the art would accept "without question" their statements about galanthamine's effects. Pls. Br. at 46-47. Instead, Plaintiffs argue that the patent provides "existing data in the prior art

to establish utility." *Id.* at 47. But, as noted in Defendants' Opening Brief, Plaintiffs' disclosure of five articles, none of which addresses the utility of galanthamine for treating AD, does not suffice to prove utility. As to the animal model disclosed in the specification, Plaintiffs admit that, at best, it provided an "expectation of utility," because the testing with galanthamine had never been done. *Id.* This yet-to-be executed research, however, was nothing more than a plan to experiment rather than the data required to show utility and enablement. Such a "plan" is insufficient. *See Northpoint Tech., Ltd.*, 413 F.3d at 1310.[25] Because there is no dispute that Dr. Davis provided absolutely no data regarding the use of galanthamine to treat AD, and one of ordinary skill would not accept without question that galanthamine could be used to treat AD, the '318 patent is not enabled and thus invalid.[26]

C. Plaintiffs' Nicotinic Theory of Enablement Fails

As a last ditch effort to save the patent from itself, Plaintiffs repeat in their brief the same desperate argument presented for the first time at trial[27] regarding their belief that the patent

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[25] Plaintiffs' citation to *In re Brana*, 51 F.3d 1560, cuts against their argument. *In re Brana* concerned whether certain tests were inadequate to satisfy the utility inquiry. Although Plaintiffs cited *In re Brana* to suggest that an inventor may rely on prior art to establish utility, the court found significant that the applicants *had* supplied "test results showing that several compounds within the scope of the claims exhibited significant antitumor activity against the L1210 standard tumor model *in vivo*." *Id.* at 1567. That is, the patentee produced data based on specific animal tests. The court then noted that prior art also tested "structurally similar compounds which were proven *in vivo* against various tumor models to be effective as chemotherapeutic agents." *Id.* Only then did the court conclude that "proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility." *Id.* No such similar testing was performed and no similar data was presented in the '318 patent.

[26] The entire range of Claim 4 also is not enabled. Contrary to Plaintiffs' assertion, *ICI* is not limited to new compounds. *Imperial Chem. Indus.,PLC v. Danbury Pharmacal, Inc.*, 777 F. Supp. 330, 373-75 (D. Del. 1991). Further, it would not have been a matter of routine experimentation to enable the full scope of Claim 4. As the Court aptly noted, "titration would be very tricky with galanthamine because there are no immediate effects, just a slowing of an inevitable decline." 1417:18-21. In attacking obviousness, according to Plaintiffs, there was nothing in the prior art about using galanthamine to treat AD, and thus Plaintiffs cannot rely upon the same prior art to establish that the full scope of Claim 4 is enabled. Once again, these inconsistent positions by Plaintiffs cannot be reconciled.

[27] Defendants have moved to strike the testimony of Dr. Raskind regarding this newly-hatched theory because that theory was not in Dr. Raskind's expert report, thus violating this Court's rules. Since Plaintiffs filed a separate response on this issue, Defendants are filing herewith a separate Reply, as recently permitted by the Court.

disclosed a nicotinic receptor theory that showed the utility of the patent thereby satisfying the enablement requirement. This argument fails.

First, this "nicotinic receptor theory" is not articulated anywhere in the two columns of the patent. Second, Plaintiffs can point to no written publication at any time setting forth such a theory, including any publications written by Drs. Davis, Coyle or Raskind. Finally, Dr. Davis never disclosed such a theory to the PTO during the prosecution of her patent. Thus, the nicotinic receptor theory is demonstrably an *ex post facto* rationale for why galanthamine would work to treat AD. Therein lies the reason for Plaintiffs' inconsistent positions at trial. On the one hand, Plaintiffs vehemently argue that the prior art did not make using galanthamine to treat AD obvious. On the other hand, because the patent contains absolutely nothing to show that galanthamine is useful, Plaintiffs are forced to argue that the prior art provides utility. That inconsistency is the same one the Court heard throughout this case and the one Plaintiffs simply cannot escape.

CONCLUSION

As set forth herein and in Defendants' Opening Post-Trial Brief, Defendants have presented clear and convincing evidence that the '318 patent is anticipated by Bhasker and is obvious under *KSR*. Should the Court disagree that using galanthamine to treat AD is obvious, the patent is not enabled as those of ordinary skill in the art would not have accepted without question that galanthamine could be used to treat AD, nor did the inventor provide Dr. Davis provide any data in her patent showing as much. As such, the '318 patent is invalid.

Respectfully submitted,

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